Amendments to the Specification

Please replace the paragraph at page 4, lines 20-31 with the following amended paragraph:

A self-emulsifying drug delivery system (SEDDS) having improved bioavailability has recently been developed for the compounds of formula (I), as described in U.S. Application No. 10/357,919 (S. Chen et al.), filed February 4, 2003, now U.S. Patent No. 6,828,301, and in PCT/US03/03380 (Boehringer Ingelheim Pharmaceuticals, Inc.), filed February 5, 2003, published as WO 03/066103 A1. This formulation comprises a compound of formula (I), about 0.1 to 10% by weight of a pharmaceutically acceptable amine or a mixture of pharmaceutically acceptable amines, one or more pharmaceutically acceptable oils, optionally one or more pharmaceutically acceptable hydrophilic solvents, optionally one or more pharmaceutically acceptable polymers, and optionally one or more pharmaceutically acceptable surfactants. However, it has been found that this formulation may not be fully optimized with respect to its chemical stability and therefore may require storage under refrigerated conditions.

Please replace the Brief Description of the Drawings section appearing at page 7, lines 17 to 25, with the following amended section:

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the impurity profile of a formulation according to the present invention containing tromethamine and sodium hydroxide (Formulation # 2) and a comparative formulation without sodium hydroxide (Formulation # 1) when both formulations were subjected to stability testing for 5 days at 70°C. This figure shows that the level of major degradation product 1 is lower in Formulation # 2 than in comparative Formulation # 1.

Figure 2 shows the impurity profile of a second formulation according to the present invention containing tromethamine and sodium hydroxide (Formulation # 3) and a comparative formulation without sodium hydroxide (Formulation # 1) when both formulations were subjected to stability testing for 5 days at 70°C. This figure shows that the

level of major degradation product 1 is lower in Formulation # 3 than in comparative Formulation # 1.

Please replace the paragraph at page 17, lines 7 to 22 with the following amended paragraph:

Pharmaceutically acceptable oils useful in the composition includes a broad spectrum of water-immiscible materials such as, for example, medium or long chain mono-, di- or triglycerides, vegetable oils such as soybean oil, avocado oil, squalene oil, sesame oil, olive oil, canola oil, corn oil, rapeseed oil, safflower oil, and sunflower oil, fish oils, flavored oils, water insoluble vitamins, fatty acids, and mixtures thereof. More preferred oils include mono-, di- or triglycerides of caprylic fatty acids; mono-, di- or triglycerides of capric fatty acids; oleic acid, and mixtures thereof. Some preferred oils include those commercially available under the trade names: ~~Capmul~~CAPMUL® MCM, ~~Capmul~~ CAPMUL® MCM C-8, ~~Capmul~~ CAPMUL® MCM C-10, ~~Capmul~~ CAPMUL® PG-8, ~~Miglyol~~MIGLYOL® 810, ~~Captex~~CAPTEX® 355, ~~Miglyol~~ MIGLYOL® 812, ~~Captex~~ CAPTEX® 200, ~~Myvacet~~MYVACET®, ~~Myverol~~MYVEROL® 18-92, ~~Maisine~~MAISINE®, and ~~Arlacel~~ARLACEL® 186. The amount of oil(s) in the composition may vary over a wide range and the optimum amount for a particular composition will depend on the type and amount of other the other ingredients in the composition as can be determined by the skilled pharmaceutical technician. In general, however, the pharmaceutically acceptable oil is present in an amount of from about 1% to 99% by weight, more preferably in an amount of from about 20% to 70% by weight.

Please replace the paragraph at page 18, lines 4 to 13 with the following amended paragraph:

To adjust the viscosity of the formulations or to improve stability, pharmaceutically acceptable polymers can optionally be used in the composition, which include, for example, polyethylene glycols (e.g., PEG 1000, PEG 1500, PEG 3350, PEG 6000 and PEG 8000), polyvinylpyrrolidones (e.g., ~~Kollidon~~KOLLIDON® 12 PF, ~~Kollidon~~ KOLLIDON® 17 PF, ~~Kollidon~~ KOLLIDON® 25 PF, ~~Kollidon~~ KOLLIDON® 30 PF, ~~Kollidon~~ KOLLIDON® 90 PF etc.), polyvinylalcohols, cellulose derivatives (e.g., hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC)), polyacrylates, polymethacrylates, sugars (e.g., lactose), polyols, and mixtures thereof. When used in the composition, the pharmaceutically

acceptable polymer is preferably be present in an amount up to about 50% by weight, preferably about 1 to 20% by weight.

Please replace the paragraph at page 18, lines 15 to 23 with the following amended paragraph:

To facilitate self-emulsification, pharmaceutically acceptable surfactants can optionally be used in the composition, which include, for example, vitamin derivatives such as Vitamin E TPGS (d-alpha tocopheryl polyethylene glycol 1000 succinate), polyoxyl castor oils (e.g., ~~Cremophor~~ CREMOPHOR® EL), polyoxyl hydrogenated castor oils, polysorbates (e.g., ~~Tween~~ TWEEN® 80), peglicol 6-oleate, polyoxyethylene stearates, polyglycolyzed glycerides (e.g., ~~Gelucire~~GELUCIRE® 44/14) or poloxamers (e.g., ~~Pluronic~~PLURONIC® F68), sodium lauryl sulfate and mixtures thereof. Preferred surfactants include Vitamin E TPGS, polyoxyl 40 hydrogenated castor oil or polyoxyl 35 castor oil, and mixtures thereof.

Please replace the paragraph at page 19, line 22 to page 20, line 2 with the following amended paragraph:

A further particular embodiment of the SEDDS composition according to the present invention is directed to a pharmaceutical composition, comprising:

(a) about 10% to 20% by weight of a compound of formula (I);
(b) about 0.1% to 5% by weight of tris(hydroxymethyl)aminomethane;
(c) about 0.1% to 3% by weight of sodium hydroxide;
(d) about 20% to 70% by weight of a triglyceride of caprylic fatty acid or a triglyceride of capric fatty acid, or mixtures thereof;
(e) about 10% to 30% by weight of a mixture of propylene glycol, ethanol and optionally water;
(f) optionally about 1% to 20% by weight of polyethylene glycol or polyvinylpyrrolidone; and
(g) about 20% to 50% by weight of d-alpha tocopheryl polyethylene glycol 1000 succinate or polyoxyl 35 castor oil ~~(Cremophor EL)~~.

Please replace the paragraph at page 20, lines 4-15 with the following amended paragraph:

A further particular embodiment of the SEDDS composition according to the present invention is directed to a pharmaceutical composition, comprising:

(a) about 10% to 15% by weight of a compound of formula (I);

(b) about 0.1% to 2% by weight of tris(hydroxymethyl)aminomethane;

(c) about 0.1% to 1% by weight of sodium hydroxide;

(d) about 20% to 30% by weight of ~~Capmul MCM~~ medium chain mono- and diglycerides or ~~Captex 355~~ medium chain triglyceride;

(e) about 15% to 25% by weight of a mixture of propylene glycol, ethanol and water; and

(f) about 40% to 50% by weight of d-alpha tocopheryl polyethylene glycol 1000 succinate; and

(g) about 0.01% to 1% of dl-α-tocopherol.

Please replace the table appearing from the bottom of page 38 to the top of page 39 with the following amended table:

Formulation #1 (comparative)

Ingredient	Weight (mg/g)	%(w/w)
Compound #822	100	10
Tromethamine	10	1
Water	20	2
Ethanol	100	10
Propylene glycol	50	5
Alpha-Tocopherol	4	0.4
~~Capmul~~CAPMUL® MCM	220	22
V_E TPGS	516	49.6

Please replace the table appearing at the top of page 39 with the following amended table:

Formulation #2

Ingredient	Weight (mg/g)	%(w/w)
Compound #822	100	10
Tromethamine	10	1
Sodium hydroxide	3	0.3
Water	17	1.7
Ethanol	100	10
Propylene glycol	50	5
Alpha-Tocopherol	4	0.4
~~Capmul~~ CAPMUL® MCM	220	22
V_E TPGS	516	49.6

Please replace the table appearing at page 39, lines 5 to 10, with the following amended table:

Formulation #3

Ingredient	Weight (mg/g)	%(w/w)
Compound #822	100	10
Tromethamine	10	1
Sodium hydroxide	3	0.3
Water	30	3
Ethanol	100	10
Propylene glycol	50	5
Alpha-Tocopherol	4	0.4
~~Captex~~ CAPTEX® 355	220	22
V_E TPGS	483	48.3

Please replace the paragraph at page 39, line 11 to page 40, line 2 with the following amended paragraph:

Preparation of Formulations 1-3:

First, the liquid components such as ~~Capmul~~ CAPMUL® MCM, ~~Captex~~ CAPTEX® 355, propylene glycol, alpha-tocopherol, water and ethanol were mixed together in a tightly closed container. V_E TPGS was melted at 40°C and then transferred into the container.

And then tromethamine and/or sodium hydroxide solution was added to the above mixture. Finally, Compound #822 was added to the container and stirring was continued at 40°C until the drug was completely solubilized. These formulations can be filled into hard shell or soft gelatin capsules.